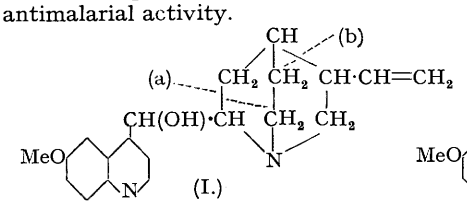
39. *Synthetic Antimalarials. Part XIII. Some N-Dialkylaminoalkylamidines.*

By F. H. S. Curd and C. G. Raison.

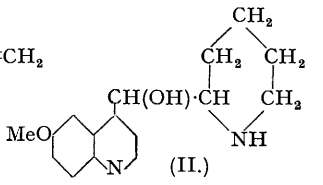
In an attempt to dispense with the heterocyclic structure of mepacrine, series of *N*-β-diethylaminoethylarylamidines and *N*-β-diethylaminoethyl-*N'*-arylarylamidines have been prepared, but none of the compounds exhibited any activity against avian malaria.

The present investigation was commenced at about the same date as that described in Part I (Curd and Rose, *J.*, 1946, **343**), but for various reasons reporting has been delayed. Although none of the compounds now described possesses any antimalarial activity, some of the concepts underlying this investigation have been usefully developed in other directions.

Ainley and King (*Proc. Roy. Soc.*, 1938, *B*, **125**, 60) have shown that the quinine molecule (I) can be simplified to give 4-(6-methoxyquinolyl)-2-piperidylcarbinol (II) with retention of antimalarial activity.



(I.)



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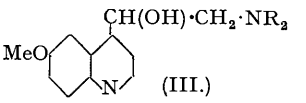


(III.)

Later King and Work (*J.*, 1940, 1307) synthesised some quinolylcarbinolamines of the type (III), and again antiplasmodial activity was found in the compounds (when R = C_4H_9, C_5H_{11}, or C_6H_{13}).

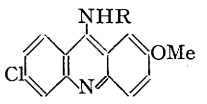
Compounds of type (III) may be regarded as derived from quinine (I) (or more closely dihydroquinine) by fission of the quinuclidine portion of the molecule along the lines (a) and (b), and the retention of activity suggested that simplification of the mepacrine molecule (IV; R = CHMe·$[CH_2]_3$·NEt_2) might also lead to active structures. Indeed, it was known that compounds of types (V) and (VI) (R = dialkylaminoalkyl), which can themselves be regarded as portions of the mepacrine molecule, possessed antimalarial activity (Schönhöfer, *Z. physiol. Chem.*, 1942, **274**, 1; G.P. 683,692). Now Schönhöfer (*loc. cit.*) has suggested that the tautomeric system (VII) $\rightleftharpoons$ (VIIa), found in mepacrine and also in (V) and (VI), is important for antimalarial activity, and for further simplification of (V) or (VI) retention of a similar tautomeric system seemed therefore to be desirable.

It is possible to regard the tautomeric system (VII) $\rightleftharpoons$ (VIIa) as an extended amidine system RNH–C=CH–CH=N– $\rightleftharpoons$ RN=C–CH=CH–NH–, and by the principle of vinylogy (Fuson, *Chem. Reviews*, 1935, **16**, 1) the system RNH–C=N– $\rightleftharpoons$ RN=C–NH– is equivalent;

this suggested simplification of (V) to the amidine (VIII; R = Cl, R′ = dialkylaminoalkyl) and of (VI) to (IX; R = dialkylaminoalkyl). Accordingly (IX; R = $[CH_2]_2$·NEt_2) and a series of compounds of type (VIII; R′ = $[CH_2]_2$·NEt_2) with a variety of substituents (R) in the benzene nucleus were prepared.

E.P. 481,814 describes *inter alia* 4-dialkylaminoalkylamino-7 : 8-benzoquinolines (X) and variously substituted derivatives of the same type which by a similar process of modification lead to naphthamidines of the type (XI; R′ = dialkylaminoalkyl); a number of compounds of this type were also prepared. Mention is made in the same patent of azabenzoquinolines (phenanthrolines), and in consequence an aza-derivative (XII) of type (XI) was synthesised.

Although none of the compounds of types (VIII), (IX), (XI), and (XII) exhibited any antiplasmodial activity (*P. relictum* and *P. gallinaceum* tests) it was decided to explore a somewhat similar modification of the mepacrine molecule itself, and the preparation of (XIII; R = Cl, R′ = OMe, R″ = CHMe·$[CH_2]_3$·NEt_2) and (XIV) was projected, on the basis of simplifying the extended to a normal amidine system in the two possible ways with retention of either the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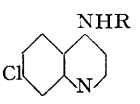
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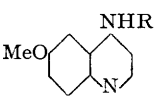
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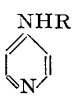
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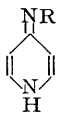
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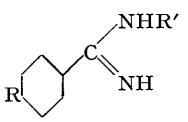
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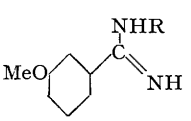
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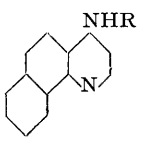
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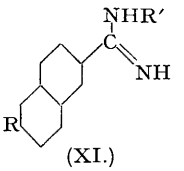
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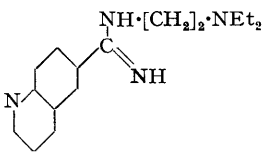
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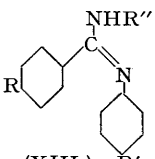
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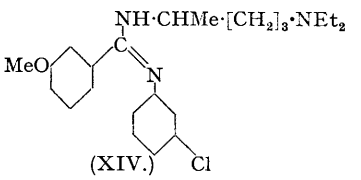
(XIV.)

p-anisidine or the *m*-chloroaniline unit which is the remaining component of the mepacrine molecule. The investigation was, however, abandoned before the synthesis of these actual compounds had been effected; a number of compounds of the same general type such as N′-p-*chlorophenyl*-N-β-*diethylaminoethyl*-p-*methoxybenzamidine* (XIII; R = OMe, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) were however made, but all failed to show any antiplasmodial activity against *P. gallinaceum* in chicks.

The amidines of types (VIII), (IX), (XI), and (XII) were prepared by the well-established method from the corresponding cyanides, which were converted into the iminoethyl-ether hydrochlorides followed by interaction with β-diethylaminoethylamine in alcoholic solution. The synthesis of the related *N*-arylamidines is illustrated by that of N′-p-*chlorophenyl*-N-β-*diethylaminoethylbenzamidine* (XIII; R = H, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) which was obtained from benz-*p*-chloroanilide by conversion, with phosphorus pentachloride, into the iminochloride, and interaction of this with β-diethylaminoethylamine.

Experimental.

m-*Methoxyphenyl Cyanide*.—This has been prepared previously from *m*-methoxybenzamide by Bailar (*J. Amer. Chem. Soc.*, 1930, **52**, 3596), but he gave no experimental details.

m-Methoxybenzaldehyde (Posner, *J. pr. Chem.*, 1910, **82**, 431) (73 g.) was stirred with alcohol (125 c.c.), and a solution of sodium hydroxide (26·8 g.) in water (60 c.c.) added followed by hydroxylamine sulphate (55·3 g.). The temperature rose to 60°, was maintained at 60—70° for ½ hour, and the mixture then left to cool overnight. It was diluted with water (1·5 l.) and acidified with acetic acid, and the oxime extracted with ether. Removal of the ether from the dried extract left an oil (63 g.) which was refluxed for 5 hours, with stirring, with a mixture of acetic anhydride (570 c.c.) and fused sodium acetate (93 g.), and then poured into water (1·25 l.). When the acetic anhydride had decomposed the liquid was cooled, treated with anhydrous sodium carbonate (500 g.), and extracted with ether. The extract, after being washed with sodium carbonate solution and water and dried, was evaporated to yield the cyanide as a

colourless liquid, b. p. 116—120°/13 mm. (yield, 45 g.) (Found : C, 71·7; H, 5·2. Calc. for C_8H_7ON : C, 72·2; H, 5·3%).

2-*Cyano*-6-*methoxynaphthalene*.—A mixture of 2-bromo-6-methoxynaphthalene (Franzen and Stäuble, *J. pr. Chem.*, 1922, **103**, 352) (25 g.), cuprous cyanide (10·7 g.), and pyridine (9·3 g.) was heated at 180—190° for 15 hours. The reaction mixture was dissolved in hot pyridine (70 c.c.) and the solution poured into ammonia (*d* 0·088, 145 c.c.) and water (435 c.c.) with stirring. The resulting suspension was well shaken with ether and, after filtration, the ether was washed with dilute hydrochloric acid, then with water, dried, and evaporated. Crystallisation of the residue from light petroleum (charcoal) yielded the *compound* as colourless needles, m. p. 104—106° (yield, 67%) (Found : C, 78·2; H, 4·7; N, 7·6. $C_{12}H_9ON$ requires C, 78·7; H, 4·9; N, 7·65%).

6-*Hydroxy*-2-*cyanonaphthalene*.—Attempts to prepare this by a Sandmeyer reaction on 6-amino-2-naphthol were not very successful, the best yield obtained being 13%. The reaction between 6-bromo-2-naphthol and cuprous cyanide in the presence of pyridine was unpromising. This may have been due to a reaction involving the phenolic group, since when this was acetylated a cyanide was readily obtained.

6-Bromo-2-acetoxynaphthalene (m. p. 110—111°; lit. m. p. 103°) (107 g.), cuprous cyanide (41·4 g.), pyridine (35·9 g.), and a trace of anhydrous copper sulphate (cf. Koelsch and Whitney, *J. Org. Chem.*, 1941, **6**, 795) were heated with stirring at 180—190° for 8 hours. The mixture was then dissolved in hot pyridine (220 c.c.), added to a stirred solution of sodium cyanide (150 g.) in water (1·5 l.), and the mixture extracted with ether. The extract, after being washed with dilute hydrochloric acid and water, was dried (Na_2SO_4) and evaporated to leave a solid (62 g.), m. p. *ca.* 110—120°, which appeared to be a mixture of 2-cyano-6-acetoxynaphthalene and the required cyanonaphthol. It was added to a stirred and cooled solution of potassium hydroxide (36 g.) in methanol (220 c.c.); it dissolved rapidly and in a short time a crystalline precipitate began to separate. After being stirred for 1 hour the mixture was diluted with water to 1 l., and the solution clarified by ether extraction and then acidified with hydrochloric acid. The precipitate, washed and dried in ether solution followed by evaporation of the solvent, was crystallised from aqueous alcohol to yield the *cyanonaphthol* (yield, 62%), m. p. 164—166°. It separated from benzene in colourless prisms, m. p. 166—167° (Found : C, 78·1; H, 3·9; N, 8·2. $C_{11}H_7ON$ requires C, 78·1; H, 4·1; N, 8·2%).

When the crude substance, m. p. 110—120°, was crystallised, first from aqueous methanol and then several times from benzene–petrol, pure 2-*cyano*-6-*acetoxynaphthalene* was obtained (yield, ca 33%) as colourless plates, m. p. 102—103° (Found : C, 74·2; H, 4·2; N, 6·6. $C_{13}H_9O_2N$ requires C, 73·9; H, 4·3; N, 6·6%).

6-*Bromo*-2-*cyanonaphthalene*.—Ice water (250 c.c.), surrounded by an ice and salt mixture, was stirred whilst hydrochloric acid (70 c.c.) followed by an aqueous solution of sodium nitrite (7·5 g.) was added. A cold solution of 6-bromo-2-naphthylamine (22·2 g.) in acetic acid (120 c.c.) was then added in a rapid thin stream with vigorous stirring. The acidity of the diazonium solution to Congo red was removed by the addition of sodium acetate, and the solution was then run into a stirred solution of cuprous cyanide in sodium cyanide [from copper sulphate (50 g.)] at 70—80°. After cooling, the product was filtered off and digested with a mixture of equal parts of concentrated hydrochloric acid and water, washed, dried, and extracted with boiling alcohol (500 c.c.). The filtered extract was evaporated and the residue crystallised from benzene–methanol and then from alcohol to give the *compound* (yield, 22%) as stout orange needles, m. p. 160—162° (Found : C, 56·6; H, 3·2; N, 6·1. $C_{11}H_6NBr$ requires C, 56·9; H, 2·6; N, 6·0%).

The other cyano-compounds used were made by literature methods.

Preparation of Imino-ether Hydrochlorides.—A solution or suspension of the cyano-compound (1 mol.) in dry chloroform containing absolute alcohol (3—4 mols.) was saturated at 0° with hydrogen chloride and left at room temperature for a few days. After evaporation to dryness under reduced pressure at 30°, the last traces of hydrogen chloride were removed in a desiccator. The yields were approximately quantitative. With the exception of *p*-acetamidobenzimino-ether hydrochloride which was extremely hygroscopic, the imino-ether hydrochlorides were colourless solids stable at room temperature and were not subjected to any further treatment before use. 6-Methoxy-2-naphthimino-ether formed a *dihydrochloride* (Found : Cl, 23·7. $C_{14}H_{15}O_2N,2HCl$ requires Cl, 23·5%).

N-*β-Diethylaminoethylamidines*.—The compounds listed in Table I were prepared by stirring the appropriate imino-ether hydrochloride (1 mol.) with 8—10 times its weight of absolute alcohol containing *β*-diethylaminoethylamine (1·05 mols.) for 8 hours at 40—45°. The alcohol was then removed under reduced pressure at 30° and the residue treated with water and sufficient hydrochloric acid to make the solution acid to Congo-red. After being warmed for a short time the solution was cooled, and any non-basic material removed by filtration or extraction with ether. The acid solution was then evaporated under reduced pressure at 40°, the last traces of water being removed by repeated evaporation with benzene–alcohol. In cases where the hydrochloride failed to crystallise conversion to either the hydrobromide or the nitrate gave a crystalline salt. After *p*-acetamidobenziminoether hydrochloride had been condensed with *β*-diethylaminoethylamine in the above manner and the alcohol removed, the residue was deacetylated by boiling with 7% hydrochloric acid for 3 hours. The yield of amidine was usually 75—80%.

Iminochlorides.—The iminochlorides from benz-*p*-chloro-, -*p*-methoxy-, -*m*-chloro-, and -3 : 5-dichloroanilides were made according to Chapman (*J.*, 1927, 1743; 1932, 1770); those from 2 : 4-dichlorobenz-*p*-anisidide (m. p. 40—42°) and *p*-methoxybenz-*p*-chloroanilide (m. p. 90—92°), which appear to be new compounds, were prepared in the same way but were not analysed.

N′-*Aryl*-N-*β-diethylaminoethylamidines*.—The appropriate iminochloride (1 mol.) was added to a solution of *β*-diethylaminoethylamine (1 mol.) in 12 times its weight of alcohol cooled to − 10°, and after being stirred below 0° for 3 hours the mixture was warmed slowly to 40—45° and maintained at this temperature for 8 hours. The alcohol was then removed under reduced pressure at 30°, and the residue treated with aqueous sodium hydroxide and extracted with ether. The ether extract was shaken with 5% acetic acid, the acid extract rendered alkaline with sodium hydroxide, and the liberated amidine again extracted with ether. Evaporation of the dried (K_2CO_3) ether extract left the amidine

TABLE I.

N-*Diethylaminoethylamidines*, $CHR(:NH)\cdot NH\cdot CH_2\cdot CH_2\cdot NEt_2$.

Ref. No.	Nature of R.	Formula.	M. p.	Analysis. Found (%). C.	H.	Cl.	Required (%). C.	H.	Cl.
2563	*p*-Anisyl	$C_{14}H_{23}ON_3,2HCl$ (EtOH–EtOAc)	214—216° (decomp.)	52·9	8·05	22·2	52·2	7·8	22·05
2564	*m*-Anisyl	$C_{14}H_{23}ON_3,2HBr$ (EtOH–EtOAc)	180—181 (decomp.)	40·5	5·9	38·5 (Br)	40·9	6·1	38·9 (Br)
2565	*p*-Chlorophenyl	$C_{13}H_{20}N_3Cl,2HCl,H_2O$ (EtOH–EtOAc)	244—246 (decomp.)	45·1	6·9	31·4	45·3	6·9	30·9
2566	6-Methoxy-2-naphthyl	$C_{18}H_{25}ON_3,2HCl$ (EtOH)	221—223 (decomp.)	58·2	7·3	19·1	58·1	7·3	19·1
2567	Phenyl	$C_{13}H_{21}N_3,2HBr$ (EtOH)	234—235 (decomp.)	41·2	5·75	41·2 (Br)	41·0	6·0	42·0 (Br)
2568	6-Hydroxy-2-naphthyl	$C_{17}H_{23}ON_3,2HCl,\frac{1}{2}H_2O$ (EtOH)	257—259 (decomp.)	55·4	7·4	18·9	55·6	7·1	19·3
2586	*p*-Hydroxyphenyl	$C_{13}H_{21}ON_3,2HNO_3$ (EtOH–EtOAc)	148—150 (decomp.) after sintering at 130—135	43·8	6·8	19·2 (N)	43·2	6·4	19·4 (N)
2622	2-Naphthyl	$C_{17}H_{23}N_3,2HBr$ (EtOH)	228—230 (decomp.)	47·0	6·3	36·4 (Br)	47·3	5·8	37·1 (Br)
2634	*p*-Aminophenyl	$C_{13}H_{22}N_4,3HCl$ (EtOH–H_2O–$COMe_2$)	Decomp. 284	46·1	7·5	30·5	45·4	7·3	31·0
2636	6-Quinolyl	$C_{16}H_{22}N_4,3HBr$ (MeOH–EtOAc)	259—261 (decomp.)	37·2	5·0	46·0 (Br)	37·4	4·9	46·8 (Br)
2766	6-Bromo-2-naphthyl	$C_{17}H_{22}N_3Br,2HCl$ (MeOH–EtOAc)	Indef. 235—250, then decomp.	48·3	5·7	1 mg. ≡ 1·14 mg. AgX	48·5	5·7	1 mg. ≡ 1·13 mg. AgX

TABLE II.

N′-*Aryl*-N-*diethylaminoethylamidines*, $CR(:NR')\cdot NH\cdot CH_2\cdot CH_2\cdot NEt_2$.

Ref. No.	R.	R′.	Formula.	M. p	Analysis. Found (%). C.	H.		Required (%). C.	H.	
2660	Phenyl	*p*-Chlorophenyl	$C_{19}H_{24}N_3Cl,2HNO_3$ (EtOH)	Decomp. 154°	50·0	5·65	15·05 (N)	50·05	5·7	15·4 (N)
3175	,,	*p*-Anisyl	$C_{20}H_{27}ON_3,2HI$ (EtOH)	181—183	41·15	5·2	43·0 (I)	41·3	5·0	43·7 (I)
3176	,,	3 : 5-Dichlorophenyl	$C_{19}H_{23}N_3Cl_2,2HNO_3$ (EtOH–EtOAc)	Decomp. 147	46·5	5·1	14·5 (Cl)	46·5	5·1	14·5 (Cl)
3177	,,	*m*-Chlorophenyl	$C_{19}H_{24}N_3Cl,2HI$ (EtOH)	114—116 (decomp.)	39·5	4·3	1 mg. ≡ 0·976 mg. AgX	39·0	4·4	1 mg. ≡ 1·047 mg. AgX
3178	2 : 4-Dichlorophenyl	*p*-Anisyl	$C_{20}H_{25}ON_3Cl_2,2HI$ (EtOH–EtOAc)	237—238 (decomp.)	37·0	4·25	1 mg. ≡ 1·145 mg. AgX	36·9	4·15	1 mg. ≡ 1·165 mg. AgX
4536	*p*-Anisyl	*p*-Chlorophenyl	$C_{20}H_{26}ON_3Cl,2HI$ (EtOH)	Decomp. >150	38·9	4·85	1 mg. ≡ 0·845 mg. AgX	39·0	4·6	1 mg. ≡ 0·996 mg. AgX

base as an oil. The hydriodide or nitrate proved to be the easiest salts to crystallise. The base was converted into the salt by dissolving it in dilute acid to give a solution faintly acid to Congo-red followed by evaporation under reduced pressure, finally with the addition of alcohol–benzene. The average yield of amidine, calculated on the iminochloride, was 56%. The compounds prepared are listed in Table II.

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